Ten-year experience of whole lung lavage in pediatric Pulmonary Alveolar Proteinosis

Zehn-jährige Erfahrung mit Ganzlungenwaschung bei kindlicher Alveolar-Proteinose

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ABSTRACT

Background Pulmonary Alveolar Proteinosis (PAP) is extremely rare and can be caused by hereditary dysfunction of the granulocyte macrophage colony-stimulating factor receptor (GM-CSF) receptor, autoantibodies against GM-CSF, or other diseases leading to alveolar macrophage (AM) dysfunction. This leads to protein accumulation in the lung and severe dyspnea and hypoxemia. Whole lung lavage (WLL) is the first line treatment strategy.

Methods Here, we present data from more than ten years of WLL practice in pediatric PAP. WLL performed by the use of a single lumen or double lumen tube (SLT vs. DLT) were compared for technical features, procedure time, and adverse events.

Results A total of n = 57 procedures in six PAP patients between 3.5 and 14.3 years of age were performed. SLT based WLL in smaller children was associated with comparable rates of adverse events but with longer intervention times and post-procedural intensive care treatment when compared to DLT based procedures.

Discussion Our data shows that WLL is feasible even in small children. DLT based WLL seems to be more effective, and our data supports the notion that it should be considered as early as possible in pediatric PAP.

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Conclusion WLL lavage is possible in small PAP patients but should performed in close interdisciplinary cooperation and with age appropriate protocols.

ZUSAMMENFASSUNG

Hintergrund Die pulmonale Alveolarproteinose (PAP) ist eine sehr seltene Lungenerkrankung welche durch Mutationen im Granulozyten-Makrophagen-Kolonie-stimulierenden Faktor (GM-CSF)- Rezeptorgen, durch GM-CSF-Autoantikörper oder durch andere Erkrankungen mit Schädigung der Alveolarmakrophagenfunktion hervorgerufen wird. Dies führt zu Proteinakkumulation in der Lunge und schwerer Hypoxämie und Atemnot. Die Ganzlungenlavage stellt die Therapie der ersten Wahl dar.

Methoden Hier zeigen wir Daten einer Zehnjahresbeobachtung von Ganzlungenlavagen bei Kindern mit PAP. Wir vergleichen Ganzlungenlavage-Prozeduren mittels Einzellumen- versus Doppellumen-Tubus im Hinblick auf Durchführung, Dauer und Komplikationen.

Resultate Insgesamt wurden n = 57 Prozeduren bei sechs PAP Patient:innen im Alter zwischen 3,5 und 14,3 Jahren ausgewertet. Einzellumen-basierte Lavagen wurden bei jüngeren Kindern durchgeführt und zeigten vergleichbare Komplikationsraten, aber längere Interventions- und längere postinterventions-Behandlungsdauern auf der Kinderintensivstation.

Diskussion Wir zeigen, dass Ganzlungenlavagen auch bei kleinen Patient:innen durchführbar sind, wobei Doppellumentubus-basierte Prozeduren bei PAP im Kindesalter schneller zu sein scheinen und daher, wenn möglich, frühzeitig versucht werden sollten.

Schlussfolgerung Ganzlungenlavagen sind möglich und relativ sicher bei jungen PAP-Patient:innen, aber sollten in einem erfahrenen Zentrum in enger interdisziplinärer Kollaboration und mit alters-angepassten Protokollen durchgeführt werden.

Introduction

Pulmonary Alveolar Proteinosis (PAP) is a severe lung disease characterized by disturbed surfactant protein homeostasis in the alveoli [1]. It may be caused by mutations in the granulocyte macrophage colony stimulating factor receptor (GM-CSF-R) gene, autoantibodies against GM-CSF, or by other causes like infection or drug induced lung injuries. This leads to disturbed alveolar macrophage (AM) maturation and function and disruption of surfactant protein homeostasis with protein accumulation in the alveoli, impaired gas exchange and lung inflammation. PAP can cause respiratory failure with hypoxemia and, as the disease progresses, irreversible damage to the lung parenchyma. Due to AM malfunction, PAP patients are at increased risk for severe lower respiratory tract infections [2]. Whole-lung lavage (WLL) is the first line treatment option for PAP today, although promising additional therapeutic approaches have been reported in recent years [3–5]. Due to the rarity of the disease, only few centers are experienced in performing WLL in children and adolescents [6, 7]. In adults double lumen tube (DLT) based WLL is the standard technique [8]. However, DLT based WLL can only be performed in older children and adolescents.

Here, we report our experiences in pediatric PAP-patients by analyzing retrospectively data from more than ten years of pediatric WLL. We describe our techniques and compare incidences of adverse events and postprocerural complications between SLT- versus DLT-WLL.

Methods

Collection of clinical and WLL data

All PAP patients were treated at Hannover Medical School and were included into the European registry for children´s interstitial lung diseases "ChILD-EU" after written informed consent was obtained by legal guardians. Demographic and clinical data as well as information on bronchoscopic procedures and adverse events were retrospectively obtained from clinical records as well as from the prospectively collected data from ChILD-EU. Data were collected using a dedicated data base, employing Excel (Microsoft Office V 2010; Microsoft, Redmond/WA, USA) and a Filemaker (V18; Claris, Cupertino/CA, USA) based system.

WLL procedure and anaesthesiologic management

All WLL procedures were performed by or under the supervision of an experienced specialist in pediatric pulmonology as well as a dedicated pediatric anaesthesthesiology team with expertise in this field. After positioning of the patient on the operating table, standard monitoring consisting of electrocardiography, non-invasive blood pressure measurement and pulse oximetry was established (Carescape B850; GE Healthcare, Boston/MA, USA). Intravenous access was obtained prior to each procedure. A conductive warming air blanket (Moeck Warming System, Moeck, Hamburg, Germany) was used to preserve normothermia during the procedure, which was monitored (Carescape B850; GE Healthcare, Boston/MA, USA).

Anaesthesia was induced by injection of 3–5 mg/kg propofol, 0.5 µg/kg remifentanil and 0.5 mg/kg atracurium and maintained by total intravenous anaesthesia (TIVA) with propofol and remifentanil. Volatile anaesthetics were avoided to reduce exposure risks for the staff. Anaesthesia depth was monitored by EEG (Narcotrend, MT Monitor GmbH & Co. KG, Hannover, Germany). Since 2015, standard monitoring was expanded to regional cerebral oxygen saturation ($rSpO_2$) measurements using near infrared spectroscopy (INVOS, Medtronic, Dublin, Ireland). Endexpiratory Carbon Dioxide (CO_2) and body temperature monitoring was carried out throughout the entire procedure. Intraarterial measurement of blood pressure was performed in most interventions. Hourly blood-gas analysis were performed in each procedure, with shorter intervals once a $tcPCO_2$ of 80 mmHg was reached. Transcutaneous CO_2 pressure ($tcpCO_2$) monitoring (TINA Radiometer TCM 4, Copenhagen, Denmark) was employed in most WLL procedures.

Patients were intubated by single lumen tube (SLT) Microcuff-Tubus® 4.5–6.0 Inner diameter (ID) (AVANOS MEDICAL, Alpharetta, USA)

as well as Rüschelit®Super safety clear 5.5–6.5 ID (TELEFLEX, Dublin, Ireland) for children up to a tube size of 6.5 ID. For WLL, a wire-guided Arndt endobronchial blocker (AB) 5 French (F) or 7 F (Cook Medical; Bloomington/IND, USA CooK Medical) was then positioned under bronchoscopic view in the main bronchus of the lung undergoing washing. A 1,8 mm rhinoscope was positioned directly proximal to the main carina to continuously monitor the correct position of the AB and to reposition it immediately in case of dislocation.

For children with airways large enough to place a 6.5 mm SLT, a left-sided double lumen endotracheal tube (DLT; Rüsch Bronchopart Telefax Medical, Dublin, Ireland) with size 26–32 Charriere (Ch) was applied. The correct position of the DLT was visualized by a 2.8 mm bronchoscope after intubation. Ventilation was provided during the intervention with the Primus® work station (Drägerwerk AG & Co. KGaA, Lübeck, Germany). Peak pressures of up to 35 mbar were tolerated in the ventilator settings in the lungs that had not yet been rinsed.

Setting and tubing systems used in DLT based WLL with are illustrated in Supplementary Fig. 1a/b.

After intubation, patients were carefully positioned on a vacuum mattress (VAC-PAC® 51608, TapMed, Habichtswald-Ehlen, Germany) in the lateral decubitus position. After that, the correct position of AB and DLT was rechecked bronchoscopically.

Pre-warmed NaCl 0.9 % was used for WLL in all procedures. Arndblocker was connected to a pressure transducer (Codan pvb Critical Care GmbH, Forstinning, Germany). This was set to zero. Then the pressure was measured step by step after the repetitive application of irrigation fluid. Via a 50 ml perfusor syringe. This should not exceed 20 cm H2O. The irrigation fluid was then withdrawn again with the perfusor syringe. In patients with DLT-ventilation, the lavage fluid freely ran into the lung from a 5 Liter (l) bag reservoir, suspended approximately 20 cm above the lung to be washed until a pressure of 20 cm H_2O.

Before the lavage fluid was drained from the lungs, dissolution of proteins was supported by gentle vibrations applied to the patient´s thorax (Vibrax Senator Professional®, Arends, Offenbach, Germany). WLL was briefly interrupted in case of severe hypercapnia and/or hypoxemia and a two-lung ventilation was performed until the values recovered. The lower saturation limit for interruption of the WLL was approximately 85 % for approximately 15 minutes. Lavage was continued until broncho-alveolar lavage fluid (BALF) retrieval was significantly less opaque than prior fractions (Suppl. Fig. 1c) which corresponded to a significant reduction in protein outflow (Suppl. Fig. 1d). In some cases, BALF was analysed for total protein content using the Bradford assay (Coomassie Plus Assay Kit®; Thermo Fisher, Waltham/MA, USA) according to the manufacturer´s recommendations.

After rinsing of the first lung, the procedure was temporarily interrupted and the patient was ventilated for 15 to 30 minutes with a positive end expiratory pressure level (PEEP) of 8–10 cm H_2O until blood-gas analyses showed clear increase of arterial oxygen pressure (paO_2) and decrease of arterial carbon dioxide pressure ($paCO_2$). Then, the patient was repositioned to the contralateral decubitus, and lavage of the contralateral lung was performed.

Postinterventionally in SLT based WLL the AB was removed, and in DLT WLL, ventilation was switched to SLT ventilation. Patients were transferred to PICU and ventilated with PEEP levels of 8–10 mbar to avoid pulmonary edema and monitored for several hours. Extubation was usually performed after ventilation parameters had stably returned to normal.

Definition of severe adverse effects of WLL

Severe complications were defined as events such as severe hypoxia with a drop in SpO2 < 80 %, hypercapnia > 80 mmHg and resuscitation leading to an interruption of the procedure.

Statistical analyses

Calculations and graphs were generated using Excel (Microsoft Office V 2019; Microsoft, Redmond/WA, USA) or GraphPad Prism (V5; Claris, GraphPad, San Diego/CA, USA). Depending on data distribution, two tailed T-test or Mann-Whitney-U-testing was applied to compare different groups, and p values < 0.05 were considered significant.

Ethics

All patients and/or their legal guardians gave consent for systematic analysis and publication of this data. This analysis was approved by the local ethics committee of Hannover Medical School.

Results

In total, data from 10.5 years (June 2011 until January 2022) and n = 57 WLL procedures were analyzed. During this period, six patients underwent WLL due to hereditary (n = 4), autoimmune (n = 1) or postinfectious (n = 1) PAP. Four patients were female, two were male. ▶ **Table 1** summarizes demographic and etiological patient data. The mean age at first WLL at our center was 10.1 years (range 3.5 to 14.3 years, body weight range 10 to 52 kg), and the mean observational period per patient was 3.7 years (range 0.2 to 7.8

▶ **Table 1** Patient characteristics and main adverse events (f: female, m: male, yr.: year; observ.: observational period; SLT: single lumen tube; DLT: double lumen tubes; WLL: whole lung lavage) * (< 1 yr. observ.)

	Gender	*Type of PAP*	*Age at first lavage[yrs.]*	*Observational period yr*	*WLL procedures (total; mean/yr.)*	*Min-max (WLL/yr.)*
ID 1	f	*hereditary*	*3.5*	*7.8*	*27; 3.3*	*1–8*
ID 2	f	*hereditary*	*8.7*	*5.0*	*22; 5.5*	*5–6*
ID 3	f	*autoimmune*	*10*	*0.2*	*2 **	*2 **
ID 4	m	*post viral*	*12.9*	*1 timepoint*	*1;1*	*1*
ID 5	f	*hereditary*	*14.3*	*1.8*	*3/2*	*1–2*
ID 6	m	*hereditary*	*11.3*	*1 timepoint*	*1;1*	*1*

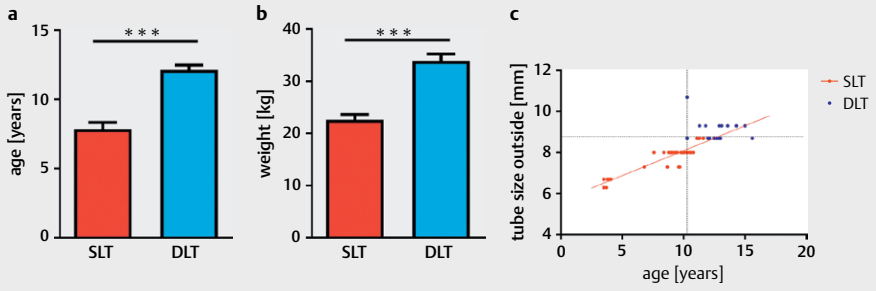
years). A mean of 2.2 WLL per calendar year and patient (range 1 to 5) were performed.

Overall, n = 40 SLT based and n = 17 DLT based WLL procedures were analyzed. Children undergoing SLT-WLL were significantly younger and had lower body weight compared to those undergoing DLT based procedures (mean age 7.8 vs. 12. 1 years of age ($p < 0.01$); mean weight 22.6 vs. 33.9 kg, $p < 0.01$; ▶ **Fig. 1a/b**). The mean age to switch from SLT to DLT-based procedures were 10.3 years (▶ **Fig. 1c**).

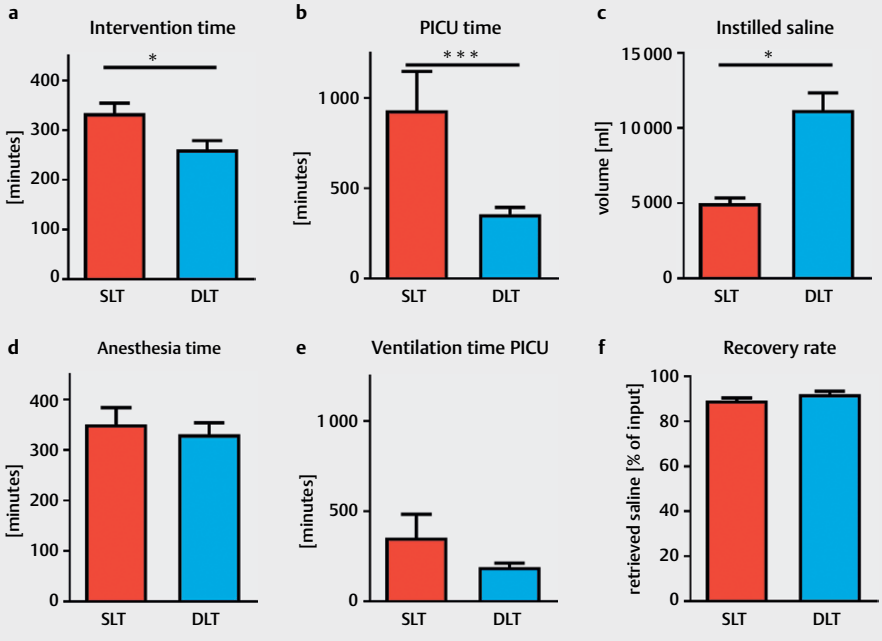
Intraveneous anesthesia was performed in all patients using propofol with mean peak doses of 9.7 mg/kg/h (range 5 to 12,4 mg/kg/h) and remifentanil 0.26 µg/kg/min (range 0.1 to 0.5 µg/kg/min), respectively. In 70.2 % (n = 40) of the interventions the catecholamine regime was run with epinephrine or norepinephrine, in 10.5 % (n = 6) with dopamine and in 8.8 % (n = 5) with ephedrine. In only 10.5 % (n = 6) of WLL procedures, no catecholamine therapy was needed.

The outer diameter (OD) of 8.7 mm in an SLT corresponds to the smallest available DLT with 26 Ch. N = 40 WLL procedures were performed SLT based (6.3–8.7 mm OD) and n = 17 were performed through a DLT (8.7–10.7 mm OD). In eight procedures, an 8.7 mm OD (6.5 ID) SLT was chosen even if DLT intubation would have been possible (▶ **Figure 1c**). This was done due to specific anatomic considerations to avoid possible injuries

With regard to single lung ventilation parameters during the WLL procedures, our analyses revealed a mean tidal volume of 5.04 ml/kg (range 3.43–6.43 ml/kg) and a mean maximum pressure (Pmax) of 31.58 mbar (range 19.0–40.0 mbar) with a mean PEEP of 5 mbar (range 4.0–10.0 mbar).



▶ **Fig. 1** Age and weight at SLT vs DLT-based WLL procedures: significantly lower age (**a**) and weight (**b**) of children undergoing WLL with SLT. Correlation of age (**c**) with tube sizes used for intubation to perform WLL (dotted lines represent mean age appropriate for intubation with size 6.5 needed for DLT-WLL, bars in A and B display mean +SEM, C: linear regression with 95 %-CI, in * * *: $p < 0.001$).



▶ **Fig. 2** Procedure times and rinsing volumes in SLT- vs. DLT-based WLL: Longer intervention time (**a**) and lower amounts of saline rinsed into the lungs (**e**) of children undergoing SLT-based WLL, but comparable saline recovery rates (**f**) and overall anesthesia times (**b**) in both settings. Significantly longer PICU times after SLT as compared to DLT-WLL (**d**), but comparable ventilation times on the PICU (**c**), bars display mean +SEM, *: $p < 0{,}05$, * * *: $p < 0.001$).

▶ **Table 2** Detailed description of patients suffering severe adverse events and the measures take. Abbreviations: AB = Arndt-blocker; bpm = beats per minute; ECG = echocardiography; ID = inner diameter; min = minutes;tcpO2 = transcutane oxygen saturation; VV-ECMO = veno-venous extracorporal membrane oxygenation

Patient	Age (yr)	Tube	Complication	Measures
ID 1	3,8	SLT	SpO_2 drop to 40 % while anesthesia induction due to laryngospasm, decrease of heart rate to 70 bpm	1 min chest compressions 0.1 mg atropine, Intubation
	3,9	SLT	CO_2retention up to 148 mmHg in blood gas analysis with ST-lowering in ECG	pausing single-lung ventilation, lowering pCO_2, change of tube from 4.5 to 5.0 ID Normalisation of transthoracic-ECG
	8,9	SLT	SpO_2 drop of 4 min to 46–61 % and 5 min to 40–56 %	pausing single-lung ventilation
	9	SLT	Dislocation AB with SpO_2 drop to 61–72 % for 4 min	Aspiration of lavage fluid and pause of single lung ventilation followed by repositioning of AB
ID 2	8,7	SLT	Dislocation of AB with SpO_2 drop to 56–74 % for 9 min, recurrent bradycardia SpO_2 drop to 55–67 % for 7 min	1 min chest compressions, 3 × 200 µg epinephrine, 0.2 mg atropine Transthoracic-ECG: right ventricular heart failure Establishment of VV-ECMO Continuation of the procedure with ECMO therapy Postinterventional invasive mechanical ventilation for 2 days and ECMO support for 3 days 5 days on intensive care unit
	10,1	SLT	SpO_2 drop to 65–79 % for 5 min	pausing single lung ventilation
	13	DLT	SpO_2 drop to 70–78 % for 6 min	pausing single lung ventilation
ID 3	10,3	DLT	SpO_2 drop to 59–66 % for 4 min Ventilation problems with low AZV. persistent hypercapnia	pausing single lung ventilation termination of the procedure after lavage of only one side

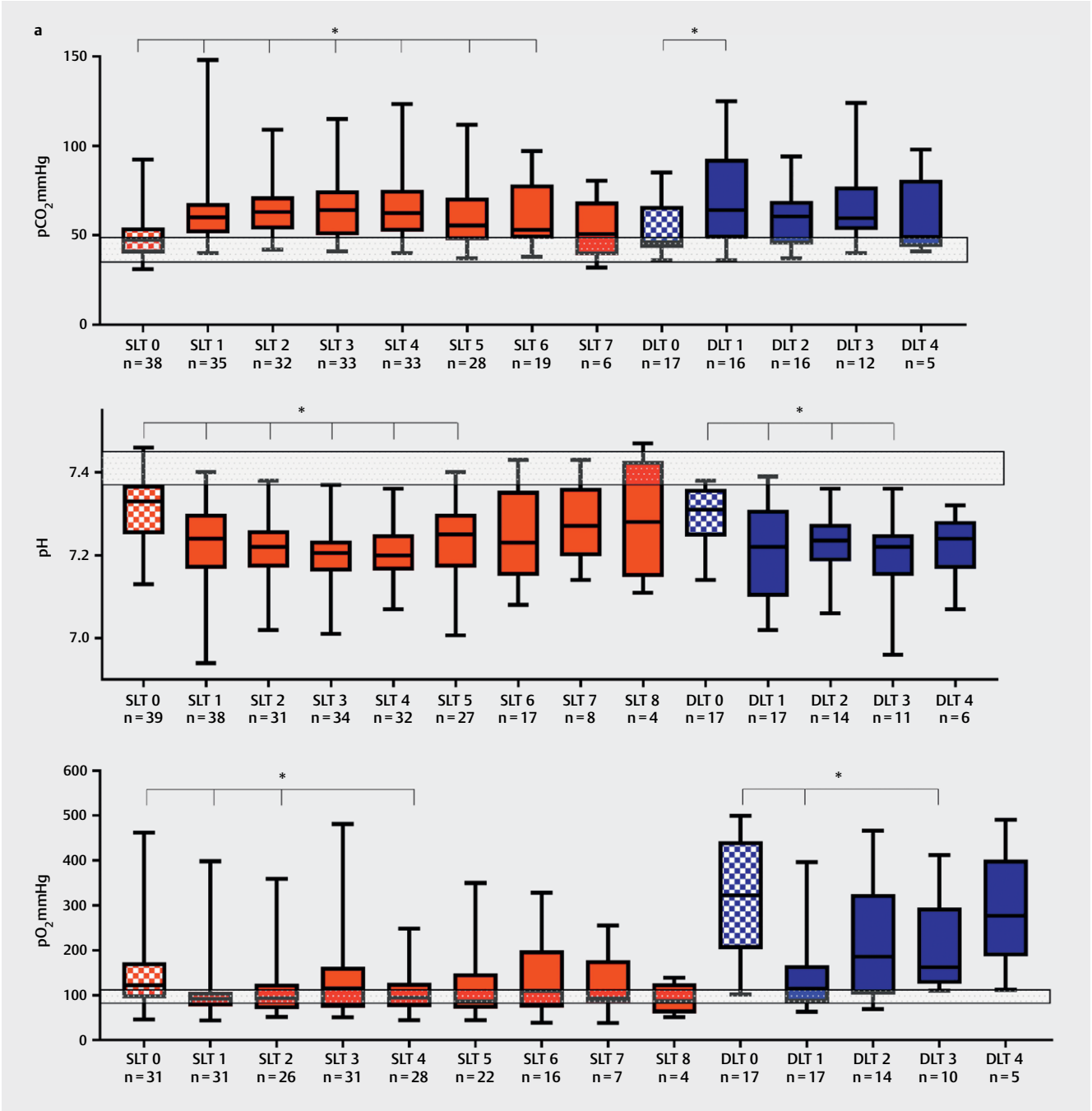
Next we analyzed procedure and periinterventional treatment times. While durations of WLL were significantly shorter in patients rinsed with a DLT system (mean of 5.6 vs. 4.4 hours, $p < 0.05$, ▶ **Fig. 2a**), overall anesthesia time in the operation room did not differ significantly between the two groups (mean of 5.9 and 5.5 hours, respectively, ▶ **Fig. 2d**).

The mean total volume used to rinse both lungs was 7.5 L per procedure (range 1.2–24 L), Significantly less saline was used in smaller children in SLT based as compared to DLT based interventions (mean of 4.9 vs. 11.2 L, $p < 0.01$, ▶ **Fig. 2c**). The mean recovery rate as assessed by weighing the outflow of lavage fluid was 91.3 % (range 86 to 96.2 %), and no significant difference in the recovery rate was between these techniques occurred (mean of 89.4 vs. 92.1 %, ▶ **Fig. 2f**).

With regard to postproderural treatment on the pediatric intensive care unit (PICU), a mean of 11.6 PICU-hours (range 2.7 to 116.5) were spent after WLL procedures. The mean duration of postinterventional ventilation was 5 hours (range 0.3 to 68.2 hours). Children undergoing SLT-based procedures stayed significantly longer on PICU than those after DLT-based WLL (mean of 15.5 vs. 5.9 hours, $p < 0.01$, ▶ **Fig. 2b**) and needed longer postinterventional ventilation times (mean of 5.9 vs. 3.2 hours, p 0.59, ▶ **Fig. 2e**).

As shown in Suppl. Figure 3, hypoxemia and bradycardia during WLL typically occurred in waves, synchronized with the maximum influx of saline into the rinsed lung. Accordingly, most patients transiently experienced hypoxaemia (SpO2 < 90 %) or severe hypoxaemia (SpO2 < 80 %, 72.5 %/ 52.5 % of SLT-based procedures and 70.6 %/ 58.8 % of DLT-based procedures), which was treated by changing ventilation parameters without interrupting the procedure. Serious adverse events (SAE) leading to procedure interruption such as hypoxemia < 80 %, severe hypercapnia or cardiac arrest were reported in eight of the procedures (14 %) in 3 patients (▶ **Table 2**). SAEs occurred 15 % of SLT based procedures and 11.7 % of WLL with the DLT system. The frequency of severe complications is comparable. In two patients (ID 1 and 2), short cardiac arrest with demand for chest compressions occurred. In one of these cases (ID2, procedure with SLT at the age of 8.7), the transfer of irrigation fluid to the contralateral lung assumingly led to a sudden, strong increase in pulmonary arterial pressure resulting in low ventricular output, hypotension and coronary underperfusion, leading to short term cardiac arrest the transient need of extracorporeal membrane oxygenation (ECMO) support. The second cardiac arrest (ID1, procedure with SLT at the age of 3.8) was also of short nature and occurred after a sudden SpO_2 drop to 40 % during anesthesia induction prior to WLL.

In three further cases severe hypoxia ($SpO_2 < 80$ % with need for switch to double lung ventilation ID1, procedure with SLT at the age of 8.9; ID 2 procedure with SLT at the age of 10,1 and procedure with DLT at the age of 13)) occurred. One procedure (ID3, procedure with DLT at the age of 10,3) with persistently insufficient oxygenation and strong $paCO_2$ increase despite adaptation of ventilator support was terminated prematurely after only one lung side had been lavaged (▶ **Table 2**). Importantly, all patients that experienced severe complications during WLL recovered completely and did not suffer from transient or long-term sequelae. Hypercapnia (as defined as $paCO_2 \geq 46$ mmHg) occurred in all patients in at least one WLL. Across all analyzed WLL procedures, the highest mean $paCO_2$ level during WLL was 75.2 mmHg (range 38–148). The highest recorded value of 148 mmHg paCO2 (ID 1 procedure with SLT at the age of 3.9) was accompanied by ST wave depression in the ECG (▶ **Table 2**). It could be lowered again by pausing the WLL procedure and re-intubating from a 4.5 to 5.0 mm ID tube to reduce airway resistance. The ST–lowering normalized.

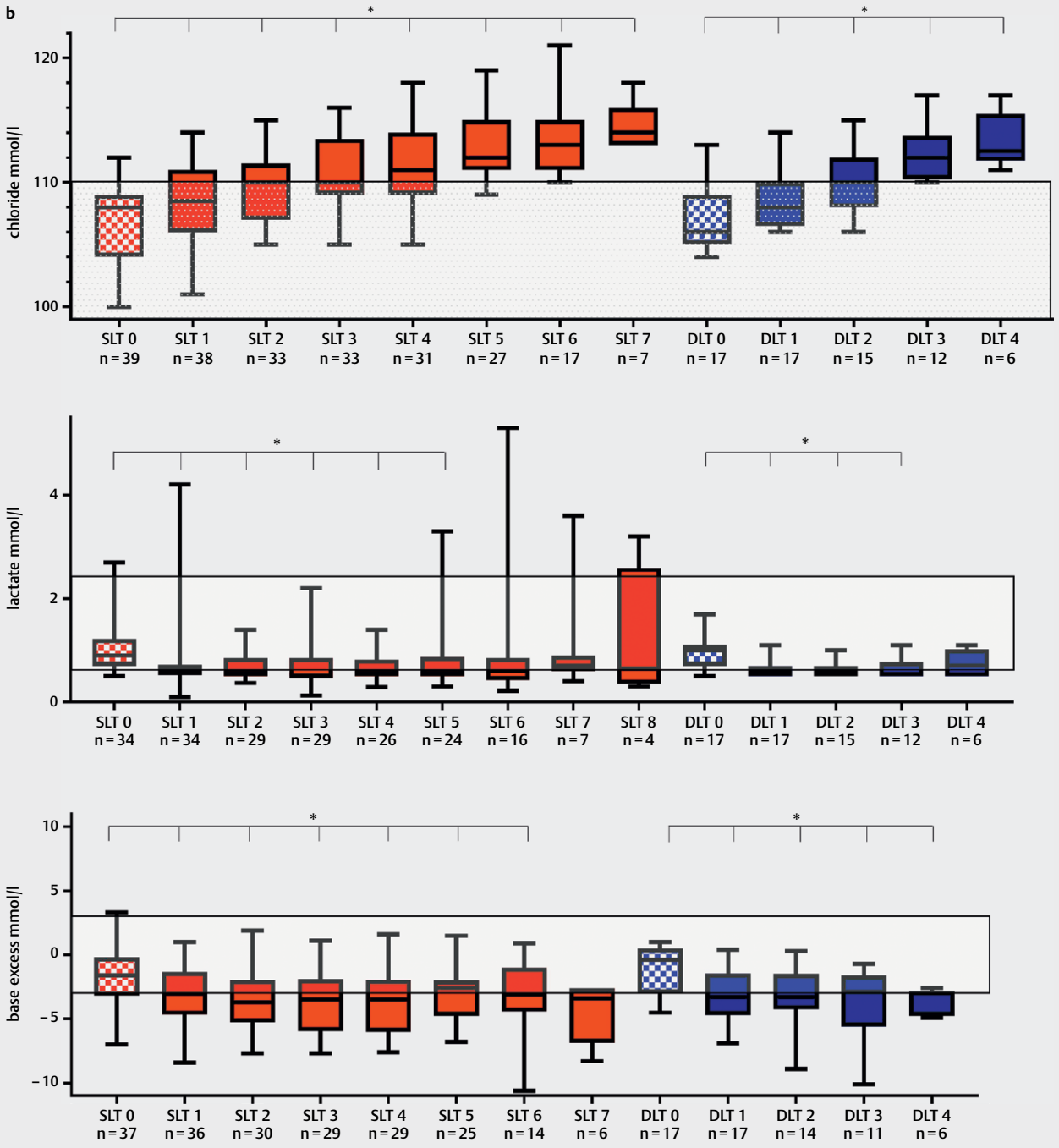


▶ **Fig. 3** **a**: Blood gas analyses pCO2, pH, pO2 during WLL procedure (SLT- (red) and DLT-based (blue), initial value (checkered)). Number of individual examinations are noted under each bar, blood gas analysis were not performed every hour for all patients, boxplots display min,Q1, median, Q3, max, light grey boxes show normal range * : p < 0,05.

When assessing blood gas analyses over time in PAP patients undergoing SLT or DLT based WLL, we observed an increase in $paCO_2$ and initial decrease in paO_2 over time, which was partially compensated by the end of the procedures. This was accompanied by transient decrease in pH and base excess levels over time, which also typically normalized by the end of WLL (▶ **Fig. 3a + b**).

As NaCl-based WLL can theoretically lead to increased chloride levels and lactat acidosis, we analyzed chloride levels over time, which indeed significantly increased over the time courses in both SLT- and DLT-WLL (▶ **Fig. 3b**). However, this was not accompanied by lactate acidosis (▶ **Fig. 3b**).

When we next analyzed blood gas parameters that were obtained during postinterventional observation on the PICU, we saw a decrease in $paCO_2$ and stable paO_2 levels over time, which was accompanied by a normalization in pH, lactate, and base excess and chloride levels (Suppl. Fig. 2a + b) in patients after both SLT and DLT based WLL.



▶ **Fig. 3** **b**: Blood gas analyses lactate, base excess and chloride during WLL procedure (SLT- (red) and DLT-based (blue), initial value (checkered)). Number of individual examinations are noted under each bar, blood gas analysis were not performed every hour for all patients, boxplots display min,Q1, median, Q3, max, light grey boxes show normal range * : p < 0,05.

Discussion

To our knowledge, the here presented analysis represents the largest and most comprehensive dataset on WLL in children with PAP published thus far. We show that WLL can be performed even in young children starting from an age of 3.5 years, and that the procedure is relatively safe, despite the sometimes severely compromised condition of the children at the time of WLL procedure. For small children with PAP, we show that sequential blocking of the lungs in an SLT ventilated child can be performed safely and with good rinsing recovery. However, SLT WLL was associated with longer intervention and PICU observation times in our center, and with slightly but not significantly higher rates of hypoxia and serious adverse events compared to WLL with DLT (15 % vs. 11.7) %. In our cohort, WLL was associated with an overall rate of 14 % of severe ad-

verse events comparable to the described 18 % reported by Campo et al. in a previous, similar analysis [7].

DLT based WLL was carried out in our study starting from the mean age of 10.3 years. In the literature, DLT based WLL has been suggested for children as young as eight years of age [9], but in our cohort, PAP patients were usually too small to be intubated with the smallest available commercially DLT. In our view, smaller DLT devices would be highly desirable, as our data shows that DLT WLL in children is faster and associated with a shorter PICU treatment after the procedures. This observation may be explained by several reasons. Firstly, due to the larger lumen of the DLT, DLT WLL was significantly faster. Also, cumbersome blocking and repositioning maneuvers frequently performed during SLT based WLL were by far less often needed in DLT based procedures. Two of our serious complications were caused by dislocated airway blockade in SLT WLL. The risk of tube dislocation is also considerably lower due to the structure of the DLT following the anatomical bifurcation of the trachea. However, also the older age of the children undergoing DLT WLL could have led to a less difficult overall cardiorespiratory management and lower frequency of SAE – independently of the mode of intubation.

In our experience, the switch from SLT to DLT based lavage should be considered when the children can be safely intubated with a 6.5 mm ID SLT of , as this has the same outer diameter of 8.7 mm as the smallest DLT of 26 Ch. Because currently available DLT are very rigid, prior sizing with a 6.5 mm ID SLT is reasonable. This is consistent with a publication of Chambers et al., who recommend an intubation trial with a 6.5 mm ID SLT in children who should receive a 6.0 ID tube following the empirical formula "age/4 + 3.5" to see if intubation with a 26 Ch DLT might be possible [10]. Therefore, intubation with a DLT from an SLT size of 6.0 mm ID may be considered. However, this must be done with extreme caution with regard to possible injury of the airways. However, in our view, to make WLL safer for small children, it would be very desirable to obtain a DLT < 26 Ch for smaller children.

Another important aspect to make WLL safer and more efficient for children suffering from PAP is the strong interdisciplinary collaboration and communication in the interdisciplinary team performing the procedures. The monitoring of vital parameters and blood gas analyses and regular check-ups of the correct position of tubes and rinsing fluid is a team effort which is only possible through constant communication between pediatric pneumologists and anesthesiologists. Furthermore, complications as shown in our cohort demonstrate that WLL should be performed in an interdisciplinary clinical setting which allows for immediate treatment of severe complications and ECMO support.

During WLL, large deviations from normal cardiorespiratory parameters should be expected, such as strong increases in $paCO_2$ and ventilation pressures with a Pmax up to 35 mmHg and reduced PaO_2 levels. Assumingly, the significantly increased pulmonary artery pressure during WLL with high right ventricular pressure is the main mechanism leasing to these aberrations. It can be challenging to manage complications and choose for the right pacing of WLL and which levels of hypercapnia and hypoxemia can be accepted over which periods of time. Pragmatically, we usually opted to interrupt the procedure when $paCO_2$ values of ≥ 85 mmHg were reached. Then, a 15-minute break with two-lung ventilation was taken to recover.

The high peak in ventilation pressures during WLL resulted from the combination of the underlying disease and the hydrostatic pressure of the instilled fluid. Accordingly, ventilation pressured decreased gradually during the post intervention period, when the remaining irrigation fluid was resorbed. Our data show that WLL cannot be carried out with standard, lung-protective ventilation parameters. The ventilation parameters must be titrated to result in sufficient oxygenation to avoid WLL interruptions and prolonged intervention time.

The use of NaCl 0.9 % or WLL may lead to hyperchloremic acidosis, additionally increasing pulmonary arterial resistance. Furthermore, reduced urinary output after therapy with high chloride solution such as NaCl 0.9 % has been suggested [11]. Guidelines for i. v. fluid therapy in children therefore recommend balanced whole electrolyte solutions instead of NaCl 0.9 % to avoid acid-basis imbalance and organ dysfunction [12]. Nevertheless, none of the presented cases in our cohort developed severe metabolic acidosis despite continuous increase in serum chloride during WLL, and no patient developed renal failure during or after the procedure. This, together with the fact that normal saline is available in 5 L bags, supports the use of this fluid in WLL. However, balanced electrolyte solutions may also be suitable for WLL, and a direct comparison of these two solution types in pediatric WLL could be an interesting study objective of the future.

Little is reported about SLT based WLL in very young children to date, which was a particular focus of our work and analysis in this paper. Although we observed a higher rate of SAE in our smaller PAP patients that underwent SLT-based WLL, our approach using sequential blocking of the lavaged lung may also be of interest to other centers. One case report mentioned the use of two SLT for WLL in a PAP patient with atypical anatomy [6], and another report recently described WLL in pediatric PAP supported by ECMO therapy [13]. The authors reported that their patient was too hypoxic and too small for DLT intubation, hence underwent cannulation and ECMO-treatment for WLL. It remains to speculate whether ECMO in this case could have been avoided with the use of an SLT as described in our current paper, but our paper may help to inform on WLL strategies and their risks in similar future cases.

Our work has several limitations: Firstly, our analysis is of retrospective nature with the inherent risk of incomplete or missing information. However, due to the very detailed documentation and the inclusion of patients from the ChILD-EU registry [14], the proportion of missing data is assumingly very low. Although we aimed at defining adverse events and stringently performed WLL techniques to the best of our abilities, there was no formal WLL-standard operational procedure throughout our observation time and we cannot exclude small variations in handling that may have led to diverse outcome amongst the analyzed procedures which were not captured by our data collection. Although we present a large data set on more than 50 WLL procedures, it is only based on six PAP patients which may have skewed our results. However, given the fact that PAP is an extremely rare disease, our pediatric cohort is considerably large.

In conclusion, we here describe WLL techniques, durations, and associated adverse events in a relatively large number of pediatric PAP cases. We show using SLT WLL in small and DLT WLL in older children is feasible and comparably safe but should be performed in an experienced setting. A switch from SLT to DLT should be performed as soon as possible to shorten intervention times and post-procedural intensive care treatment. We strongly advocate for the commercial availability of DLT equipment for small children with severe lung diseases.

In sum, we hope this data helps to further develop safe treatment strategies in pediatric PAP.

Contributor's Statement

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Conflict of Interest

The authors have declared that no conflict of interest regarding the current work exists.

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